18. MULTIPLE BIRTHS

Table 18.1 shows the number of twin pairs distributed by sex type and by survival for all centres except Mexico 2 and Bogotá, where, owing to a linguistic misunderstanding, the data recorded on multiple births were not comparable with those from other centres. No data from these centres are included in any calculations in this chapter. The total number of triplet and quadruplet births (63 and 1 respectively) is too small to merit much consideration and this chapter is therefore concerned mainly with twin births. It is of interest, however, to note that the so-called Hellin's law (Hellin, 1895) is approximately satisfied by these data—i.e., the ratio of single births to twin births is approximately the same as that of twin births to triplet births and of triplet births to quadruplet births. In this case these ratios of the frequencies are 1.24%: 1.26%: 1.59% respectively.

FREQUENCY OF TWINNING

The over-all frequency of twin births is about 1.24% of all pregnancies and by chance the number of MM pairs is only one greater than that of FF pairs. It follows that the over-all sex proportion in twins (M/M + F) is very close to 0.5. The highest frequency is that in Alexandria and the ratio between highest and lowest over-all twinning frequencies exceeds 3 : 1.

It is recognized that twinning frequencies in hospital births series are likely to be higher than for all births in given areas, by reason of selection for admission of mothers where twins had been recognized. The known association with hydramnios would also lead to hospital delivery. In addition the type and degree of selection vary considerably between hospitals so that comparisons of total twinning frequencies between different hospitals are hazardous. In addition, hospital births tend to include all pairs where one or both twins were stillborn whereas these may not be included in vital statistical series. As will be seen below an undue proportion of such losses are in like-sexed pairs. However, there seems no reason why there should be any difference in frequency admissions to hospital of mothers with monozygotic or dizygotic twin pairs, so that ratios are comparable between hospitals.

MONOZYGOTIC AND DIZYGOTIC TWINS

It is usually thought that geographic and/or ethnic variations in twinning frequencies are mainly determined by differences in frequencies of the dizygotic pairs. Following the usual assumption that we should expect one like-sexed dizygotic pair for each unlike-sexed pair, the numbers of monozygotic (MZ) and dizygotic (DZ) twin pairs can be estimated for each centre. These estimated numbers, the frequencies of each per 1000 pregnancies and the ratio DZ : MZ are displayed in Table 18.2. It will be seen that there is considerably less variation in the frequency of monozygotic than of dizygotic pairs. As a test for heterogeneity χ^2 for frequencies of monozygotic pairs is 12.16 (21 degrees of freedom), and $P > 0.90$; for dizygotic pairs $\chi^2 = 94.61$ (DF 21) and $P < 0.001$.

It is clear that there is little heterogeneity of the MZ frequencies. There is no correlation between the estimated frequencies of MZ and DZ pairs ($r = -0.018$).

Many writers (e.g., Guttmacher, 1953; Komai & Fukuoka, 1936; Millis, 1959; Bulmer, 1960) have discussed variations in twinning frequencies in different countries as derived from hospital birth series and vital statistical data. It is generally agreed that dizygotic twinning is less frequent in Chinese and Japanese people than in those of European origin and Bulmer (1960) and others have found a higher dizygotic rate in African peoples. There is also considerable variation of dizygotic twinning frequency within Europe and, in addition, there is some evidence of secular trends in frequencies mainly determined by DZ variation (Jeanneret & McMahon, 1962).

It will be seen that in the present data the over-all DZ : MZ ratio is 1.82 and that ratios less than unity are found in Kuala Lumpur (0.84), Singapore (0.61), Manila (0.36) and Cape Town (0.54). The last is of interest in that the Cape Town data are in respect of the so called " Cape Coloured " people who are in large part of Malay origin (Du Plessis, 1944). The DZ : MZ ratio of 1.2 : 1 from Hong Kong is rather higher, but still much below the mean value for all centres. There the people are predominantly Cantonese, whereas there are relatively few Cantonese in Singapore. The lowest ratio is from Manila, where the people are predominantly Malay.

The DZ : MZ ratios of Chinese, Malays and Indians in Singapore and Kuala Lumpur are as follows:

	Singapore	*Kuala Lumpur*	*Singapore plus Kuala Lumpur*
Number of twin pairs:			
Chinese	224	84	308
Malays	53	46	99
Indians	33	46	79
Estimated DZ:MZ ratios:			
Chinese	0.60	0.56	0.59
Malays	1.05	0.64	0.68
Indians	0.57	1.87	1.13

There is confirmation of the high DZ frequency said to occur in peoples of African origins from the Pretoria (Bantu) frequencies and for São Paulo, but there are also comparably high frequencies from areas where there is no appreciable African contribution to the gene pool, such as Melbourne, Belfast, Czechoslovakia and Yugoslavia. The highest DZ frequency of all is from Alexandria, where the Negro contribution certainly does not dominate the composition of the gene pool.

DIFFERENTIAL MORTALITY BY SEX IN TWIN PAIRS

Elsewhere we have termed stillbirths and deaths in hospital simply " mortality " to avoid inaccurate use of the term perinatal mortality. This mortality by sex in different sex-pair types is summarized in Table 18.3. It will be seen that there is, as has been found in other series, an excess of male over female deaths in all pair types, and that the highest mortalities are in the like-sexed twin pairs. Assuming that dizygotic pairs are distributed in the proportion MM : MF : FF :: 1 : 2 : 1, the estimated numbers by pair types will be as in Table 18.4.

Following the reasoning of Barr & Stevenson (1961), if it is assumed that the mortality of dizygotic (DZ) pairs is not influenced by the sex of the other foetus *in utero*, the mortality by sex in MF pairs should apply to the appropriate sexes in those of the MM and FF pairs which are dizygotic. The expected numbers of deaths by sexes, on this assumption, may be calculated by multiplying the estimated numbers of infants in MM and FF dizygotic pairs (as derived from Table 18.4) by the appropriate mortality rates derived from the MF pair data. The remaining deaths in like-sexed pairs may be assumed to have occurred in monozygotic (MZ) pairs.

These estimates are set out in Table 18.5. They appear to afford further evidence that the excess of losses in both sexes in like-sexed pairs is predominantly but not entirely due to both twins of pairs being lost in MZ pairs. The excess loss is too great to be attributable to recessive segregating genotypes and we can only conclude that there is a harmful factor associated with monozygosity which has not yet been identified.

As is well known, mortality in twins is higher than in singletons. In these data the over-all mortality is about four times higher in twins and the estimated mortality in monozygous twins is almost five times as great.

MALFORMATIONS BY FREQUENCIES IN TWIN PAIRS ACCORDING TO SEX TYPE

In Table 18.6 are distributed the numbers of major malformations occurring in the different sex-pair types. It will be seen that a substantial contribution to the higher malformation frequency in like-sexed pairs comes from such pairs where both were affected. Parallel estimates to those made in respect of mortality lead to estimates of malformation frequencies in monozygotic and dizygotic pairs (Tables 18.7 and 18.8). It would appear that monozygotic twins, in addition to suffering a higher mortality, also experience a higher malformation frequency.

TYPES OF MALFORMATIONS OCCURRING IN TWINS

The twin pairs where either or both of the twins were malformed may be identified in the Basic Tabulations by Centres booklet. They are listed, for convenience, in Table 18.9. There appears to be only one pair where the *a priori* assumption is that there were monozygous twins who had received the same mutation. Neither parent of this pair of achondroplastics was affected.

Of the remaining pairs where both were malformed a majority show similarity of abnormality. That this majority is mainly determined by similarity of genotype is strongly suggested by the occurrence of only one pair of MF twins where both were affected.

There were two pairs of conjoined twins in the series, one of males and the other of females. They are not listed in Table 18.9. There is nothing to suggest that the spectrum of malformations in twins differs from that in single births. Some aspects of twinning and specific malformations have been considered in preceding sections. The data in respect of the neural tube defects are of particular interest (section 4).

TRIPLETS AND QUADRUPLETS

The numbers of sets occurring in the different centres are shown in Table 18.1. The distribution of triplets by sex types was MMM, 15; FFF, 19; MMF, 14; and MFF, 15. The quadruplet set was MMFF. One male of an MMF set had polydactyly (NFS). One female of an MMF set had Down's syndrome and two males of an MMM set both had talipes. One female of the quadruplets had hypoplastic kidney and double ureter (L).

CORRELATIONS OF DIZYGOTIC TWIN FREQUENCIES AND THOSE OF NEURAL TUBE DEFECTS

Examination of the data showed that in the two centres where anencephalus and other neural tube defects occurred most frequently the estimated DZ twinning rate was also high. As both these frequencies are influenced by maternal age the frequencies in the 22 centres were compared after standardization for maternal age. They appear to be significantly associated. The correlation of the frequency of anencephalus and anencephalus with spina bifida (B1+B2) with that of estimated DZ twinning is $r = +0.578$, $P < 0.01$; that of the frequency of all neural tube defects (B1-B7) and dizygous twinning is $r = +0.651$, $P < 0.001$. This phenomenon has not been demonstrated previously and it is difficult to suggest any explanation except that in some way there are predisposing factors in common.

TABLE 18.1

MULTIPLE BIRTHS: TWIN PAIRS BY SEX TYPE, MORTALITY (SB + LBD) BY SEX, MEAN MATERNAL AGES AND PREGNANCY ORDERS, AND NUMBERS OF SETS OF TRIPLETS AND QUADRUPLETS

	CENTRE	Number of pairs by sex type				% of all pregs	Death (d) or survival (s) by sex in sex pair types: MM pairs			FF pairs			MF pairs				All pregnancies		Triplets and Quads (No.)	
		MM	FF	MF	T		Both s	Both d	One s One d	Both s	Both d	One s One d	Both s	Both d	M s F d	M d F s	Mean mat. age (yrs)	Mean preg. order	TR	Q
I 1	MELBOURNE	29	36	33	98	1.2	21	6	2	29	4	3	27	2	1	3	26.8	3.0	2	0
I 2	MELBOURNE	20	18	26	64	1.6	16	2	2	14	1	3	22	2	1	1	26.5	2.7	2	0
II	SAO PAULO	61	69	81	211	1.6	45	7	9	56	5	8	74	3	2	2	26.5	3.6	2	0
III	SANTIAGO	88	77	76	241[a]	1.0	67	10	11	62	6	9	62	8	2	4	27.7	4.5	4	0
IV 1	BOGOTA [b]	(81)	(82)	(2)	(165)	(0.9)	(61)	(19)	(1)	(62)	(20)	(0)	(1)	(0)	(0)	(1)	(26.0)	(3.5)	(0)	(0)
IV 2	MEDELLIN	65	63	64	192	0.9	61	3	1	53	5	5	55	4	4	1	27.9	5.0	3	0
V	CZECHOSLOVAKIA	57	47	66	170	0.8	43	9	5	40	3	4	53	3	4	6	25.7	2.2	3	0
VI	ALEXANDRIA	116	114	161	391	3.9	84	15	17	82	12	20	133	8	7	13	28.1	5.0	7	0
VII	HONG KONG	45	46	34	125[c]	1.2	40	3	2	43	1	2	29	2	2	1	29.5	3.8	3	0
VIII 1	BOMBAY	190	155	145	490	1.2	112	40	38	91	36	28	84	29	15	17	26.8	3.5	5	0
VIII 2	CALCUTTA	79	82	107	268	1.4	53	10	16	61	7	14	73	13	10	11	25.6	3.5	5	0
IX 1	KUALA LUMPUR	67	78	43	188	1.2	53	3	11	57	11	10	32	4	3	4	28.2	4.6	3	0
IX 2	SINGAPORE	119	132	59	310	0.8	103	8	8	119	5	8	49	3	5	2	28.0	4.3	3	0
X 1	MEXICO CITY	81	108	102	291	1.2	68	5	8	95	5	8	84	6	8	4	28.0	4.7	1	0
X 2	MEXICO CITY																			
XI	BELFAST	171	166	208	545	1.9	140	14	17	141	13	12	179	11	8	10	28.1	2.8	7	0
XII	PANAMA CITY	51	49	47	147	0.9	46	2	3	48	1	0	46	0	0	1	25.2	4.4	1	0
XIII	MANILA	140	131	41	312	1.0	121	14	5	107	12	12	30	6	3	2	27.7	4.0	6	1
XIV 1	CAPE TOWN	14	19	7	40	1.3	12	1	1	18	1	0	6	1	0	0	27.2	4.2	1	0
XIV 2	JOHANNESBURG	47	46	31	124	1.1	36	6	5	34	4	8	26	2	1	1	25.4	2.8	1	0
XIV 3	PRETORIA	56	56	85	197	1.9	40	8	8	33	15	8	65	7	4	9	26.8	3.4	2	0
XV	MADRID	93	81	76	250	1.2	63	19	11	55	17	9	58	11	3	4	29.8	2.5	1	0
XVI 1	LJUBLJANA	32	35	45	112	1.3	23	3	6	29	1	5	38	3	1	3	27.6	2.0	0	0
XVI 2	ZAGREB	20	32	29	81	0.9	16	0	4	30	2	0	22	2	3	2	26.3	2.0	1	0
	TOTAL	1641	1640	1566	4847	1.24	1263	188	190	1297	167	176	1247	130	87	101			63	1

[a] One pair (? sex), both malformed, is omitted.
[b] These data are *not* included in totals.
[c] One twin pair (F/? sex) is omitted.

TABLE 18.2

MULTIPLE BIRTHS: ESTIMATED NUMBERS AND FREQUENCIES OF TWIN PAIRS BY ZYGOSITY AND DZ:MZ RATIOS

CENTRE		Monozygotic twin pairs		Dizygotic twin pairs		Ratio DZ : MZ
		Estimated number of pairs	Frequency per 1000 pregnancies	Estimated number of pairs	Frequency per 1000 pregnancies	
I 1	MELBOURNE	32	4.03	66	8.31	2.06
I 2	MELBOURNE	12	3.01	52	13.04	4.33
II	SAO PAULO	49	3.35	162	11.07	3.31
III	SANTIAGO	89	3.71	152	6.34	1.71
IV 2	MEDELLIN	64	3.10	128	6.20	2.00
V	CZECHOSLOVAKIA	38	1.88	132	6.52	3.47
VI	ALEXANDRIA	69	6.90	322	32.21	4.67
VII	HONG KONG	57	5.70	68	6.80	1.19
VIII 1	BOMBAY	200	5.00	290	7.25	1.45
VIII 2	CALCUTTA	54	2.77	214	10.99	3.96
IX 1	KUALA LUMPUR	102	6.32	86	5.33	0.84
IX 2	SINGAPORE	192	4.80	118	2.95	0.61
X 1	MEXICO CITY	87	3.48	204	8.16	2.34
XI	BELFAST	129	4.50	416	14.52	3.22
XII	PANAMA CITY	53	3.31	94	5.87	1.77
XIII	MANILA	230	7.67	82	2.73	0.36
XIV 1	CAPE TOWN	26	8.41	14	4.53	0.54
XIV 2	JOHANNESBURG	62	5.49	62	5.49	1.00
XIV 3	PRETORIA	27	2.64	170	16.63	6.30
XV	MADRID	98	4.91	152	7.61	1.55
XVI 1	LJUBLJANA	22	2.44	90	10.00	4.09
XVI 2	ZAGREB	23	2.71	58	6.82	2.52
TOTAL		1715	4.41	3132	8.06	1.82
HETEROGENEITY OF FREQUENCIES		χ^2 (DF 21) = 12.16; $P > 0.90$		χ^2 (DF 21) = 94.61; $P < 0.001$		

TABLE 18.3

MORTALITY BY SEX IN SEX-PAIR TYPES IN TWINS AND IN SINGLE BIRTHS

Sex-pair type	Mortality of:	Mortality (LBD and SB) per 1000 total births (LBA, LBD and SB)
MM	Males	566/3282 = 172.5
MF	Males	231/1566 = 147.5
FF	Females	510/3280 = 155.5
MF	Females	217/1566 = 138.6
All pairs	Males	797/4848 = 164.4
All pairs	Females	727/4846 = 150.0
Both sexes		1524/9694 = 157.2
Single births	Males	9073/214645 = 43.6
	Females	7489/201828 = 38.3

TABLE 18.4

ESTIMATED NUMBERS OF MONOZYGOTIC AND DIZYGOTIC TWIN PAIRS

	Pair type			
	MM	MF	FF	Total
Dizygotic	783	1566	783	3132
Monozygotic	858	—	857	1715
Total	1641	1566	1640	4847

TABLE 18.5

ESTIMATES OF MORTALITY IN TWIN PAIRS BY SEX AND ZYGOSITY

	Males	Females
Expected numbers of deaths in like-sexed DZ pairs	$\frac{147.5}{1000} \times \frac{1566}{1} = 231$	$\frac{138.6}{1000} \times \frac{1566}{1} = 217$
Estimated deaths (SB + LBD) in MZ pairs	566 — 231 = 335	510 — 217 = 293
Estimated mortality rate (SB + LBD/ All births) per 1000 in MZ pairs	$\frac{335}{1716} \times \frac{1000}{1} = 195.2$	$\frac{293}{1714} \times \frac{1000}{1} = 170.9$

Summary: Estimated mortality per 1000 total births

Males		Females	
DZ pairs	MZ pairs	DZ pairs	MZ pairs
147.5	195.1	138.6	170.9

TABLE 18.6

MULTIPLE BIRTHS: NUMBERS OF MALFORMATIONS IN MEMBERS OF TWIN PAIRS BY SEX AND SEX-PAIR TYPE

CENTRE		Number of twin pairs with malformed members										Total affected infants		
		MM			FF			MF						
		Neither malf.	One malf.	Both malf.	Neither malf.	One malf.	Both malf.	Neither malf.	Male malf.	Female malf.	Both malf.	M	F	T
I 1	MELBOURNE	29	-	-	35	1	-	32	1	-	-	1	1	2
I 2	MELBOURNE	19	1	-	17	-	1	25	-	1	-	1	3	4
II	SAO PAULO	55	6	-	67	2	-	80	-	1	-	6	3	9
III	SANTIAGO	86	1	1	75	2	-	76	-	-	-	3	2	5
IV 1	BOGOTA	-	-	-	-	-	-	-	-	-	-	-	-	-
IV 2	MEDELLIN	61	2	2	61	2	-	62	-	1	1	7	4	11
V	CZECHOSLOVAKIA	56	1	-	45	2	-	65	1	-	-	2	2	4
VI	ALEXANDRIA	111	5	-	114	-	-	161	-	-	-	5	-	5
VII	HONG KONG	44	1	-	46	-	-	34	-	-	-	1	1	2
VIII 1	BOMBAY	187	3	-	153	2	-	145	-	-	-	3	2	5
VIII 2	CALCUTTA	79	-	-	82	-	-	106	-	1	-	-	1	1
IX 1	KUALA LUMPUR	63	4	-	77	1	-	42	-	1	-	4	1	5
IX 2	SINGAPORE	116	2	1	130	2	-	58	-	1	-	4	3	7
X 1	MEXICO CITY	80	1	-	104	4	-	96	3	3	-	4	7	11
X 2	MEXICO CITY	-	-	-	-	-	-	-	-	-	-	-	-	-
XI	BELFAST	159	10	2	161	3	2	202	3	3	-	17	10	27
XII	PANAMA CITY	49	2	-	48	1	-	45	1	1	-	3	2	5
XIII	MANILA	139	1	-	127	3	1	41	-	-	-	1	5	6
XIV 1	CAPE TOWN	14	-	-	19	-	-	7	-	-	-	-	-	-
XIV 2	JOHANNESBURG	42	5	-	41	5	-	30	-	1	-	5	6	11
XIV 3	PRETORIA	56	-	-	54	1	1	84	1	-	-	1	3	4
XV	MADRID	91	2	-	79	2	-	73	2	1	-	4	3	7
XVI 1	LJUBLJANA	31	-	1	32	3	-	42	2	1	-	4	4	8
XVI 2	ZAGREB	19	1	-	32	-	-	29	-	-	-	1	-	1
	TOTAL	1586	48	7	1599	36	5	1535	14	16	1	77	63	140

TABLE 18.7

FREQUENCIES OF MAJOR MALFORMATIONS BY SEX IN TWIN PAIRS OF VARIOUS SEX TYPES

Pair type	Major malformations in:	Frequency	Per 1000 total births (LB + SB)
MM	Males	62/3282	18.9
MF	Males	15/1566	9.6
FF	Females	46/3280	14.0
MF	Females	17/1566	10.9
All pairs	Males	77/4848	15.9
	Females	63/4846	13.0
All single	Males	2666/207533	12.8
	Females	2438/194149	12.5

TABLE 18.8

ESTIMATES OF MALFORMATION FREQUENCIES IN TWIN PAIRS BY SEX AND ZYGOSITY

	Males	Females
Expected numbers of malformations in like-sexed DZ pairs	$\frac{9.6}{1000} \times \frac{1566}{1} = 15$	$\frac{10.9}{1000} \times \frac{1566}{1} = 17$
Estimated numbers of malformations in MZ pairs	$62 - 15 = 47$	$46 - 17 = 29$
Estimated malformations rate (per 1000 total births) in MZ pairs	$\frac{41}{1716} \times \frac{1000}{1} = 23.9$	$\frac{31}{1714} \times \frac{1000}{1} = 18.1$

Summary: Estimated frequencies of malformations per 1000 total births

Males		Females	
DZ Pairs	MZ Pairs	DZ Pairs	MZ Pairs
9.6	23.9	10.9	18.1

TABLE 18.9 SPECIFIC MALFORMATIONS IN TWINS

Malformations in Both Twins

Malformation in twin 1	Malformation in twin 2
MM pairs	
Anencephalus	Absent abdominal wall; imperforate anus; talipes
CHD (NFS)	CHD (NFS)
HL/CP (NFS)	HL (NFS)
Down's syndrome	Pelvis and legs only
Talipes (B)	Talipes (B)
Hydrocephalus	Sirenomalia
FF pairs	
Achondroplasia	Achondroplasia
Polydactyly (R) (NFS)	Polydactyly (R) (NFS)
Hydrocephalus and spina bifida	Spina bifida
Down's syndrome	Anencephalus
Absent nasal bones; branchial cyst	Hypertelorism; low-set ears; clinodactyly
MF pair	
HL/CP (male)	IVSD (female)

Malformations in One Twin Only

Malformation	Number of cases
MM pairs, only one malformed	
Down's syndrome	2
Anencephalus	6
Hydrocephalus and spina bifida	2
Spina bifida	2
Congenital heart disease (various)	7
Atresia of oesophagus, etc.	2
Imperforate anus	1
Exomphalos	1
HL and HL/CP	7
Talipes (various)	9
Polydactyly (various)	3
Polydactyly-syndactyly	2
Absent ulnae	1
IVSD; renal hypoplasia	1
Absent forearms; atresia of gut; hypospadias	1
Patent ductus; hypospadias; inguinal hernia	1
	48

Malformations in One Twin Only (cont.)

Malformation	Number of cases
FF pairs, only one malformed	
Down's syndrome	2
Anencephalus	2
Hydrocephalus	2
Spina bifida	1
Cyclops	1
Congenital heart disease	2
Atresia of oesophagus	1
Imperforate anus	2
Exomphalos	2
HL and HL/CP	2
Talipes	5
Congenital dislocation of hips	1
Polydactyly	3
Polydactyly-syndactyly	1
Sirenomelia	1
Miscellaneous	8
	36
MF pairs, only female malformed	
Down's syndrome	3
Anencephalus and spina bifida	2
Spina bifida	2
Congenital heart disease	1
Imperforate anus	1
Multiple stenoses of intestine	1
Talipes	4
Congenital dislocation of hip	1
Asymmetry of face and torticollis	1
	16
MF pairs, only male malformed	
Down's syndrome	1
Hydrocephalus	1
Spina bifida	1
Congenital heart disease	2
Cleft palate	1
Polydactyly	1
Brachydactyly and malformation of hands	1
Talipes	5
Agenesis of urogenital tract and rectum	1
	14